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10/622,076	07/17/2003	**Rudolf Gilmanshin**	C0989.70054US00	1842

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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,076	GILMANSHIN, RUDOLF	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91,125,126 and 128-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91,125,126 and 128-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on May 28, 2008 is acknowledged. Claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, 125, 126, and 128-130 are currently pending. In the response, Applicant cancelled claim 127 and amended claims 1, 91, 125, 126, and 129.

Applicant's arguments filed on May 28, 2008 have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims. Accordingly, this Office Action is made FINAL.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, 126, 128, and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (Biochemical and Biophysical Research Communications (1991) 174(2): 785-789; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule, contacting the nucleic acid polymer with the conjugate, and determining a pattern of binding of the conjugate to the polymer that is not based on the catalytic activity of the

enzyme. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. Also, the nucleic acid binding enzyme and the nucleic acid tag molecule are covalently linked.

Cheng analyzed the binding between HIV-1 reverse transcriptase and a primed nucleic acid template using UV crosslinking (see abstract and pages 786-787).

Regarding claims 1, 2, 91, 126, 128, and 129, Cheng teaches a method for analyzing a nucleic acid polymer (see page 786, last paragraph – page 787, first paragraph). Here, Cheng teaches combining a nucleic acid polymer (rA_{12-18}) with a nucleic acid tag molecule (dT_{10}) and a nucleic acid binding enzyme (HIV-1 reverse transcriptase) and performing UV crosslinking. This step results in "providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule" and "contacting the conjugate with a nucleic acid polymer". The UV crosslinking step produces a covalently bound conjugate comprising the nucleic acid tag molecule and the nucleic acid binding enzyme that is contacted with the nucleic acid polymer. When the reactants are combined in solution (page 786, last paragraph), the HIV-1 RT inherently binds the nucleic acid molecule non-specifically and translocates along the polymer. Since the nucleic acid tag molecule (dT_{10}) is complementary to the nucleic acid polymer (rA_{12-18}), it binds in a sequence-specific manner to label the nucleic acid polymer. In the method of Cheng, the reverse transcriptase enzyme does not cleave the nucleic acid polymer. The analysis of the crosslinked complexes by electrophoresis (Figures 1 & 2) constitutes determining a binding pattern of the conjugate to the nucleic acid polymer. This determination is based on the detection of radioactive labels present on the nucleic acid polymer and the nucleic acid binding enzyme, and therefore, is not dependent on the catalytic activity of HIV-1 RT (see pages 786-

787 and Figures 1-2). Finally, the HIV-1 RT taught by Cheng is a nuclease since it inherently possesses RNase H activity (page 785, 1st paragraph). Therefore, Cheng anticipates the methods of claims 1, 2, 91, 126, 128, and 129.

Regarding claims 5-7 and 11, Cheng teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is a DNA, and the enzyme is a DNA polymerase (page 786, last paragraph). Also, the nucleic acid tag molecule taught by Cheng is 10 nucleotides in length (page 786, last paragraph), which is within the claimed length range of 5-50 nucleotides.

Regarding claims 14, 16, and 31, Cheng teaches that the nucleic acid binding enzyme and the nucleic acid polymer are labeled with detectable moieties, specifically radioactive labels (page 786, last paragraph). Cheng also teaches indirect detection of the nucleic acid binding enzyme by measuring the signal from the polymer in combination with the signal from a radiolabeled nucleotide substrate (dTTP) bound to the enzyme (pages 786-788 and Figures 1-2).

Regarding claims 24-26, the nucleic acid polymer taught by Cheng is neither an *in vitro* amplified nucleic acid nor an antisense molecule (page 786). Also, the nucleic acid molecule taught by Cheng (dT_{10}) does not hybridize to bacterial or viral-specific sequences.

4. Claim 125 is rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously).

Claim 125 is drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule covalently linked to a DNA repair enzyme, a helicase, or a ligase. The nucleic acid

binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined.

Fisher teaches a method for analyzing a nucleic acid polymer (such as DNA or RNA) using a conjugate consisting of a covalently linked oligonucleotide and nuclease P1 (see abstract and column 4, lines 36-64). The nucleic acid tag oligonucleotide hybridizes specifically to the nucleic acid target (column 6, lines 5-12), and the nucleic acid binding enzyme (nuclease P1) is allowed to associate non-specifically with the nucleic acid polymer. After specific hybridization of the oligonucleotide tag molecule to the nucleic acid polymer, the hybridization pattern was detected (column 4, lines 53-64). Finally, as evidenced by Chaudhry et al., the S1 and P1 nucleases used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously) in view of Kigawa et al. (US 5,965,361; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each other. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 91, 126, and 128-130, Fisher teaches a method for analyzing a nucleic acid polymer comprising

(a) providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and contacting the nucleic acid polymer with the conjugate (column 4, lines 37-53)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer (column 4, lines 37-53)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 4, lines 37-53 column 6, lines 5-23 teach that the tag molecule binds in a sequence-specific fashion)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 4, lines 46-64).

Further regarding claims 1, 91, 126, and 128-130, Fisher teaches that the nucleic acid binding enzyme binds to the nucleic acid polymer without cleavage (column 2, lines 48-61).

Regarding claims 5, 6, and 11, Fisher teaches that the nucleic acid polymer is DNA (column 8, lines 15-43), the nucleic acid tag molecule is DNA or RNA (column 4, lines 39-40), and the nucleic acid binding enzyme is a nuclease or DNA repair enzyme (column 2, lines 48-61 and column 4, lines 37-39). As evidenced by Chaudhry et al., the S1 and P1 enzymes used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Regarding claim 7, Fisher teaches a nucleic acid tag sequence of 35 nucleotides (column 6, lines 15-16), which is within the claimed length range of 5-50 nucleotides.

Regarding claim 9, Fisher teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (column 4, lines 40-45).

Regarding claim 12, Fisher teaches that the pH of the reaction is maintained above pH 7.0, thereby preventing P1 nuclease-catalyzed cleavage of the nucleic acid substrate (column 2, lines 48-54).

Regarding claims 24 and 25, the plasmid DNA target used in the Fisher method was not amplified in vitro prior to hybridization, nor were the oligonucleotide probes designed to function as antisense molecules (Example 11, column 8, lines 15-43).

Regarding claim 26, Fisher teaches probes specific for eukaryotic sequences (column 6, lines 5-12).

Regarding claims 27, 28, and 30, the P1 nuclease and oligonucleotide components of the conjugate taught by Fisher are covalently linked (column 4, lines 37-39). Therefore, the nucleic acid tag molecule is "labeled with an agent", specifically the P1 nuclease. Furthermore, although the pH of the reaction has been adjusted to prevent P1 nuclease from cleaving the nucleic acid

substrate (column 2, lines 48-54), the enzyme has not been otherwise modified (*i.e.* by mutation), and therefore, is still inherently capable of cleaving (*i.e.* modifying) a nucleic acid molecule.

Regarding claim 31, Fisher teaches detection of the hybridization products using chemiluminescence (column 4, lines 53-64). This method indirectly detects the presence of the binding agent (P1 nuclease).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease as required by claims 1, 91, 126, 128, and 129. This method is based on detection of the nucleic acid binding enzyme rather than the nucleic acid tag molecule as required by claim 130. Fisher also does not teach labeling the nucleic acid tag molecule and the nucleic acid binding enzyme with detectable moieties, such as fluorophores, to permit fluorescence in situ hybridization as required by claims 13-15 and 21-23.

Kigawa teaches methods of analyzing nucleic acids using a conjugate comprising an oligonucleotide probe and RecA (see abstract and column 4, lines 7-31).

Regarding claims 1, 2, 91, 126, and 128-130, the method of Kigawa comprises

(a) providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme and contacting the nucleic acid polymer with the conjugate (see column 4, lines 7-25 or column 17, lines 5-25, where a conjugate comprising a biotinylated nucleic acid molecule (the "nucleic acid tag molecule") and Cy3-labeled RecA (the nucleic acid binding enzyme) is added to a target nucleic acid; column 16, lines 5-45 teach preparation of the nucleic acid probe/Rec A conjugate)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer without cleavage of the polymer (column 2, lines 39-44 and column 17, lines 5-25)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 17, lines 5-25; see also column 4, lines 16-18 and column 6, lines 11-15)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 17, lines 59-67; see also column 4, lines 27-31).

Further regarding claims 1, 91, 126, and 128-130, Kigawa teaches that the binding of the conjugate to the nucleic acid polymer is determined by measuring the fluorescence of a Cy3 label attached to the RecA protein or the signal of FITC derived from the biotinylated nucleic acid tag molecule (see column 17, lines 59-67). These methods do not rely on the catalytic activity of the nucleic acid binding enzyme. Also, when the binding pattern is determined using a signal derived from the biotinylated nucleic acid tag molecule (column 17, lines 59-67), the nucleic acid tag molecule is detected.

Regarding claims 5 and 6, Kigawa teaches that the nucleic acid polymer and nucleic acid tag molecule are DNA molecules (column 4, lines 47-49 and column 5, lines 57-59).

Regarding claim 11, Kigawa teaches that the enzyme is a DNA repair enzyme (see abstract, where RecA is taught).

Regarding claims 13-15 and 27, Kigawa teaches that the nucleic acid tag molecule is labeled with a first detectable moiety (or agent) and the nucleic acid binding enzyme is labeled with a second detectable moiety (see Example 3, column 17, lines 59-67, where Kigawa teaches

that RecA is labeled with the Cy3 fluorophore and the nucleic acid tag molecule is labeled with biotin; see also column 6, lines 22-32, where Kigawa teaches labeling of the nucleic acid tag and RecA).

Regarding claim 21, Kigawa teaches detection using FISH (see Example 3, column 17, lines 59-67).

Regarding claims 22 and 23, Kigawa teaches that the detectable moiety is a fluorescent molecule and that detection proceeds using a fluorescence detection system (column 6, lines 22-25; see also column 17, lines 59-67, where FITC fluorescence derived from the biotinylated nucleic acid tag molecule is detected using a fluorescence microscope).

Regarding claims 24-26, Kigawa teaches examples of nucleic acid tag molecules that are not in vitro amplified nucleic acids (see column 16, lines 5-18; see also column 5, line 57 – column 6, line 10). Kigawa also does not teach that the nucleic acid tag molecules are antisense molecules. Finally, the probe taught by Kigawa in Example 3 is specific for a human chromosome 1 satellite III sequence (column 16, lines 5-7). This is not a bacterial or viral-specific probe.

Regarding claim 31, Kigawa teaches that the nucleic acid binding enzyme is detected indirectly, specifically by binding of an antibody specific to the enzyme (column 3, line 64 – column 4, line 5 and column 6, lines 27-32).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Kigawa to the method taught by Fisher. An ordinary artisan would have been motivated to label the nucleic acid tag molecule and/or the nucleic acid binding enzyme with detectable moieties, such as fluorophores, recognizing that these labels permitted

direct detection of the bound enzyme-oligonucleotide conjugate. An ordinary artisan would have recognized that direct detection using a fluorescent label was faster and simpler than the indirect methods relying on nuclease activity taught by Fisher. An ordinary artisan would also have been motivated to detect the bound oligonucleotide-enzyme conjugate using any detection method taught by Kigawa, including direct detection using fluorescent, chemiluminescent, or radioactive labels bound to the oligonucleotide tag molecule or the nucleic acid binding enzyme or indirect detection based on biotin and a labeled avidin molecule, recognizing that these detection methods were art-recognized equivalents useful for the same purpose. As noted in MPEP 2144.06, substitution of art-recognized equivalents is *prima facie* obvious. Since the methods of Fisher and Kigawa were directed to the same problem, namely detection of target nucleic acids using enzyme-labeled oligonucleotides, an ordinary artisan would have had a reasonable expectation of success in substituting the direct and indirect detection methods taught by Kigawa for the indirect detection methods taught by Fisher. An ordinary artisan also would have had a reasonable expectation of success in labeling nucleic acid tag molecule and/or nuclease P1 component(s) of the conjugate taught by Fisher, as suggested by Kigawa, since methods for labeling proteins and nucleic acids with fluorescent, chemiluminescent, hapten, or radioactive labels were well known in the art as evidenced by the teachings of Kigawa (column 6, line 22 – column 7, line 60). Thus, the methods of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130 are *prima facie* obvious over Fisher as evidenced by Chaudhry in view of Kigawa.

7. Claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126, and 128-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously) in view of Rye et al. (Nucleic Acids Research (1992) 20(11): 2803-2812; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined using a backbone-specific label on the nucleic acid polymer. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 91, 126, and 128-130, Fisher teaches a method for analyzing a nucleic acid polymer comprising

(a) providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and contacting the nucleic acid polymer with the conjugate (column 4, lines 37-53)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer (column 4, lines 37-53)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 4, lines 37-53 column 6, lines 5-23 teach that the tag molecule binds in a sequence-specific fashion)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 4, lines 46-64).

Further regarding claims 1, 91, 126, and 128-130, Fisher teaches that the nucleic acid binding enzyme binds to the nucleic acid polymer without cleavage (column 2, lines 48-61).

Regarding claims 5, 6, and 11, Fisher teaches that the nucleic acid polymer is DNA (column 8, lines 15-43), the nucleic acid tag molecule is DNA or RNA (column 4, lines 39-40), and the nucleic acid binding enzyme is a nuclease or DNA repair enzyme (column 2, lines 48-61 and column 4, lines 37-39). As evidenced by Chaudhry et al., the S1 and P1 enzymes used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Regarding claim 7, Fisher teaches a nucleic acid tag sequence of 35 nucleotides (column 6, lines 15-16), which is within the claimed length range of 5-50 nucleotides.

Regarding claim 9, Fisher teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (column 4, lines 40-45).

Regarding claim 12, Fisher teaches that the pH of the reaction is maintained above pH 7.0, thereby preventing P1 nuclease-catalyzed cleavage of the nucleic acid substrate (column 2, lines 48-54).

Regarding claims 24 and 25, the plasmid DNA target used in the Fisher method was not amplified in vitro prior to hybridization, nor were the oligonucleotide probes designed to function as antisense molecules (Example 11, column 8, lines 15-43).

Regarding claim 26, Fisher teaches probes specific for eukaryotic sequences (column 6, lines 5-12).

Regarding claims 27, 28, and 30, the P1 nuclease and oligonucleotide components of the conjugate taught by Fisher are covalently linked (column 4, lines 37-39). Therefore, the nucleic acid tag molecule is "labeled with an agent", specifically the P1 nuclease. Furthermore, although the pH of the reaction has been adjusted to prevent P1 nuclease from cleaving the nucleic acid substrate (column 2, lines 48-54), the enzyme has not been otherwise modified (i.e. by mutation), and therefore, is still inherently capable of cleaving (i.e. modifying) a nucleic acid molecule.

Regarding claim 31, Fisher teaches detection of the hybridization products using chemiluminescence (column 4, lines 53-64). This method indirectly detects the presence of the binding agent (P1 nuclease).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease as required by claims 1, 91, 126, 128, and 129. This method is based on detection of the nucleic acid binding enzyme rather than the nucleic acid tag molecule as required by claim 130. Fisher also does not teach labeling the nucleic acid polymer with a backbone specific label as required by claims 16 and 17. Finally, Fisher does not teach labeling the nucleic acid tag molecule with a fluorophore or a photocleaving agent as required by claims 13, 22, 23, and 29.

Rye teaches a method for detecting nucleic acid hybridization reactions using fluorescent intercalators that show strong fluorescent enhancements upon binding to double-stranded DNA (see abstract and pages 2803-2804). Rye further teaches that the intercalators "allowed sensitive

detection, quantitation, and accurate sizing of restriction fragments ranging from 600 to 24,000 bp (see abstract)."

Regarding claims 13, 16, 17, 22, and 23, the fluorescent intercalators taught by Rye are backbone-specific labels that are detected with a fluorescence detection system (see pages 2803-2804 and pages 2807-2808).

Regarding claims 28-30, as evidenced by Thompson, the fluorescent intercalating dyes taught by Rye are photocleaving agents (see column 4, lines 3-25 and column 6, lines 1-31 of Thompson).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to detect bound oliognucleotide-nuclease P1 conjugates in the method of Fisher using the fluorescent intercalators taught by Rye. An ordinary artisan would have recognized that direct detection using the backbone-specific fluorescent intercalators of Rye would have been faster and simpler than the indirect method based on nuclease P1 activity taught by Fisher. Regarding claims 1, 91, 126, and 128-130, use of the fluorescent intercalators taught by Rye in the method of Fisher would result in a detection method that is not dependent on the catalytic activity of nuclease P1. Further regarding claim 130, using the fluorescent intercalators would result in detection of the nucleic acid tag molecule rather than the nucleic acid binding enzyme. Regarding claims 16 and 17, use of the fluorescent intercalators taught by Rye in the method of Fisher would result in the nucleic acid polymer being labeled with a backbone-specific label. An ordinary artisan would have had a reasonable expectation of success in using the fluorescent intercalator taught by Rye for detection of the bound oligonucleotide-nuclease P1 conjugates in the method of Fisher since both methods were directed to the same problem - detection of

double-stranded DNA. Thus, the methods of claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126, and 128-130 are *prima facie* obvious in view of the combined teachings of Fisher as evidenced by Chaudhry in view of Rye and Thompson.

8. Claims 19, 20, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Tegenfeldt et al. (WO 00/09757; cited previously).

These claims are drawn to the method of claim 1, wherein a single molecule linear polymer analysis system is used to determine a pattern of binding of the enzyme-nucleic acid conjugate to the nucleic acid polymer.

The combined teachings of Fisher, Chaudhry, and Kigawa result in the method of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130, as discussed above.

These references do not teach the use of a single molecule linear polymer analysis system to analyze the binding of the oligonucleotide-nuclease P1 conjugate to the nucleic acid polymer.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers (see abstract).

Regarding claim 19, the system is a linear polymer analysis system (abstract).

Regarding claim 20, Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 33, the system is capable of analyzing single polymers (page 8).

Regarding claim 34, the system described by Tegenfeldt is an optical mapping system (page 7, line 33 – page 8, line 4).

Tegenfeldt teaches the above method for the specific application of sequencing a nucleic acid molecule and also expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)."

Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use the detection system of Tegenfeldt to analyze the hybridization patterns produced by the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa. Tegenfeldt expressly taught that the disclosed linear analysis system possessed several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer nucleic acid fragments (see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Fisher and Kigawa were designed for mapping applications, an ordinary artisan would have been motivated by these teachings of Tegenfeldt to substitute single molecule linear polymer analysis for FISH in order to increase the speed and efficiency of the detection step. An ordinary artisan would have also been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa. Since Tegenfeldt taught that the proposed read length is on the order of

several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the hybridization patterns generated by the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa using single molecule linear polymer analysis as taught by Tegenfeldt. Thus, the methods of claims 19, 20, 33, and 34 are *prima facie* obvious in view of the combined teachings of Fisher, Chaudhry, Kigawa, and Tegenfeldt.

9. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; cited previously) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Gite et al. (Journal of Molecular Recognition (1995) 8: 281-289; cited previously).

Claim 32 is drawn to the method of claim 31, wherein the nucleic acid binding enzyme is detected indirectly using an antibody or antibody fragment specific for the nucleic acid binding enzyme.

The combined teachings of Fisher, Chaudhry, and Kigawa result in the method of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130, as discussed above.

Regarding claim 32, Kigawa teaches detecting nucleic acid-RecA conjugates bound to a nucleic acid polymer by using an antibody specific to RecA (see column 6, lines 28-32 and column 10, line 50 - column 11, line 28). Kigawa further states, "[B]y combining the foregoing detection methods and using a combination of RecA protein having a label or ligand, an anti-RecA antibody having a label or ligand, and a secondary antibody having a label or ligand that

can be bound to the RecA antibody, it is possible to amplify a resultant signal to be much stronger than one attained by the conventional method (column 11, lines 22-28)."

However, Kigawa does not teach an antibody or antibody fragment specific to the S1 or P1 nucleases used in the conjugates of Fisher.

Gite teaches a method for purifying S1 nuclease using antibodies specific to the nuclease (see abstract and pages 282-283).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to indirectly detect the S1 nuclease in the oligonucleotide-enzyme conjugate of Fisher using an anti-S1 antibody since Kigawa taught that the use of antibody-based detection in combination with additional labels amplified the observed signal (column 11, lines 22-28). An ordinary artisan would have had a reasonable expectation of success in using anti-S1 antibody in the method, since Gite taught S1-specific antibodies (pages 282-283). Therefore, the method of claim 32 is *prima facie* obvious in view of the combined teachings of Fisher, Chaudhry, Kigawa, and Gite.

10. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Tegenfeldt et al. (WO 00/09757; cited previously).

Claim 68 is drawn to a method for analyzing a nucleic acid polymer comprising binding a covalently-linked conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme to a nucleic acid polymer and analyzing the binding using a linear polymer analysis system.

Regarding claim 68, Fisher teaches a method for analyzing a nucleic acid polymer comprising contacting a covalently-linked oligonucleotide-nuclease P1 conjugate with the nucleic acid polymer and analyzing the resulting hybridization pattern (see column 4, lines 37-64). In the method of Fisher, the nuclease binds to the nucleic acid polymer without cleavage (column 2, lines 48-62).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease. Fisher also does not teach analyzing the nucleic acid polymer using a linear polymer analysis system.

Kigawa teaches methods of analyzing nucleic acids using a conjugate comprising an oligonucleotide probe and RecA (see abstract and column 4, lines 7-31).

Regarding claim 68, the method of Kigawa comprises

(a) contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme (see column 4, lines 7-25 or column 17, lines 5-25, where a conjugate comprising a biotinylated nucleic acid molecule (the "nucleic acid tag molecule") and Cy3-labeled RecA (the nucleic acid binding enzyme) is added to a target nucleic acid; column 16, lines 5-45 teach preparation of the nucleic acid probe/Rec A conjugate)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer without cleavage of the polymer (column 2, lines 39-44 and column 17, lines 5-25)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 17, lines 5-25; see also column 4, lines 16-18 and column 6, lines 11-15)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 17, lines 59-67; see also column 4, lines 27-31).

Kigawa teaches that the binding of the conjugate to the nucleic acid polymer is determined by measuring the fluorescence of a Cy3 label attached to the RecA protein or the signal of FITC derived from the biotinylated nucleic acid tag molecule (see column 17, lines 59-67). These methods do not rely on the catalytic activity of the nucleic acid binding enzyme.

Kigawa does not teach using a linear polymer analysis system to determine the hybridization pattern of the oligonucleotide-RecA conjugate to a target nucleic acid molecule.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers (see abstract). Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 68, Tegenfeldt teaches a method (see page 9, lines 6-15) comprising (a) generating optical radiation of a known wavelength to produce a localized radiation spot, (b) passing a polymer through a microchannel, (c) irradiating the polymer at the localized spot, (d) sequentially detecting radiation resulting from interaction of the polymer with the optical radiation at the localized radiation spot, and (e) analyzing the polymer based on the detected radiation.

Tegenfeldt teaches that the above method is useful for sequencing a nucleic acid molecule or expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)."

Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Kigawa and Tegenfeldt to the method taught by Fisher. An ordinary artisan would have been motivated to label the nucleic acid tag molecule and/or the nucleic acid binding enzyme with detectable moieties, such as the fluorophores taught by Kigawa, recognizing that these labels permitted direct detection of the bound enzyme-oligonucleotide conjugate. An ordinary artisan would have been further motivated to detect the hybridization patterns resulting from the binding of the fluorescently labeled oligonucleotide-enzyme conjugate to the target nucleic acid using the linear polymer analysis system of Tegenfeldt since Tegenfeldt taught that this system offered several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer nucleic acid fragments (see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Fisher and Kigawa were designed for mapping applications, an ordinary artisan would have been motivated by these teachings of Tegenfeldt to substitute single molecule linear polymer analysis for FISH in order to increase the speed and efficiency of the detection step. An ordinary artisan also would have been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of

the method. Since Tegenfeldt taught that the proposed read length is on the order of several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the hybridization patterns generated by the method resulting from the combined teachings of Fisher and Kigawa using single molecule linear polymer analysis as taught by Tegenfeldt. An ordinary artisan also would have had a reasonable expectation of success in labeling the oligonucleotide-enzyme conjugate with a fluorophore for use in the linear polymer analysis system of Tegenfeldt, since methods for labeling proteins and nucleic acids with fluorescent labels were well known in the art as evidenced by the teachings of Kigawa (column 6, line 22 – column 7, line 60). Thus, the method of claim 68 is *prima facie* obvious in view of the combined teachings of Fisher and Tegenfeldt.

Response to Arguments

11. Applicant's arguments filed on May 28, 2008 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, and 126-129 under 35 U.S.C. 102(b) as being anticipated by Cheng, Applicant argues that the reference does not teach all of the limitations of the claims as amended. In particular, Applicant argues that Cheng does not teach "providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme" as required by independent claims 1, 91, 126, and 129, because the conjugate comprising reverse transcriptase and the dT_{10} primer is formed after the "contacting" step (see pages 10-11). In view of the cancellation of claim 127, this rejection currently applies to claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, 126, 128, and 129. Applicant's argument was not persuasive,

because the claims as written do not require the step of "providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme" to occur before the step of "contacting a nucleic acid polymer with the conjugate". As discussed above, in the method of Cheng, the providing and contacting step occur simultaneously upon mixing of the reverse transcriptase, dT_{10} primer, and rA_{12-18} template. See also MPEP 2111.01 II, which states that it is improper to read a particular order into a series of process steps when a particular order is not required or implied as a matter of logic or grammar. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Regarding the rejection of claim 125 under 35 U.S.C. 102(b) as being anticipated by Fisher as evidenced by Chaudhry, Applicant argues that Fisher does not teach all of the claimed limitations, specifically the limitation "allowing the nucleic acid binding agent to bind to the nucleic acid polymer non-specifically" (see page 11). This argument was not persuasive, because claim 125 only recites "allowing the nucleic acid binding agent to bind to the nucleic acid polymer non-specifically". The term "allowing" only requires that the nucleic acid binding agent is capable of or not prevented from binding non-specifically to the nucleic acid polymer. In other words, the term "allowing" does not require that the nucleic acid binding agent actually binds to the nucleic acid polymer. As discussed above, the method of Fisher does not prevent or prohibit non-specific binding between the nucleic acid polymer and the nucleic acid binding agent (S1 nuclease or P1 nuclease). Therefore, Fisher teaches all of the limitations of claim 125. Since Applicant's argument was not persuasive, the rejection has been maintained.

Applicant's arguments regarding the rejection of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, and 126-130 under 35 U.S.C. 103(a) as being unpatentable over Fisher in view of Kigawa,

have been fully considered, but they were not persuasive. In view of the cancellation of claim 127, this rejection currently applies to claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130. Applicant first argues that a *prima facie* case of obviousness has not been established, because the rejection does not discuss why it would be obvious to apply the teachings of Kigawa, which pertain to methods of analyzing a nucleic acid without relying upon the catalytic activity of a nucleic acid binding enzyme, to the methods of Fisher (see page 12). This argument was not persuasive, because as discussed in the rejection, it would have been obvious for one of ordinary skill in the art at the time of invention to label the S1 or P1 nuclease taught by Fisher with a directly detectable label, such as the fluorophores taught by Kigawa, in order to obtain a simpler and faster method of detecting binding to the nucleic acid polymer. In particular, an ordinary artisan would have recognized that using a label, such one of the fluorophores taught by Kigawa, would avoid the need to conduct the more complicated and time consuming detection step based on the catalytic activity of the nuclease described by Fisher.

Applicant also argues that the combined teachings of Fisher and Kigawa do not result in all of the claimed limitations, specifically, the limitation "allowing the nucleic acid binding enzyme to bind non-specifically to the nucleic acid polymer and translocate along the nucleic acid polymer" (see pages 12-13). This argument was not persuasive, because as discussed above, the term "allowing" only requires that the nucleic acid binding agent is capable of or not prevented from binding non-specifically to and translocating along the nucleic acid polymer. In other words, the term "allowing" does not require that the nucleic acid binding agent actually binds to and translocates along the nucleic acid polymer. As discussed above, the method of Fisher does not prevent or prohibit non-specific binding between the nucleic acid polymer and

the nucleic acid binding enzyme (S1 nuclease or P1 nuclease) or translocation of the nucleic acid binding enzyme along the nucleic acid polymer. Therefore, the combined teachings of Fisher and Kigawa result in all of the limitations of the rejected claims.

Finally, Applicant argues that one of ordinary skill in the art would not have had a reasonable expectation of success in applying the teachings of Kigawa to the method of Fisher, because Fisher teaches using the enzyme as a label, whereas Kigawa teaches using the enzyme as an agent to bind a nucleic acid probe to a target nucleic acid (see page 13). This argument was not persuasive, because substituting direct detection via fluorescent labels as taught by Kigawa for the indirect detection method taught by Fisher would have been expected to amount in a reasonable level of success. The rejection does not suggest substituting the function of the enzyme taught by Fisher as a label; it only suggests that the means by which the enzyme is detected is substituted (i.e. direct detection with a fluorescent label coupled to the enzyme versus indirect detection based on the catalytic activity of the enzyme). As noted above, since labeling methods were well established in the art and discussed by Kigawa, an ordinary artisan would have had a reasonable expectation of success in directly labeling the S1 or P1 nuclease with a fluorescent label as suggested by the implicit teachings of Kigawa. Since Applicant's arguments were not persuasive, the rejection of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130 under 35 U.S.C. 103(a) as being unpatentable over Fisher in view of Kigawa has been maintained.

Applicant's arguments regarding the following rejections have been fully considered, but they were not persuasive: (1) the rejection of claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, and 126-130 under 35 U.S.C. 103(a) as being unpatentable over Fisher as evidenced by Chaudry in

view of Rye and further in view of Thompson, (2) the rejection of claims 19, 20, 33, and 34 under 35 U.S.C. 103(a) as being unpatentable over Fisher as evidenced by Chaudhry in view of Kigawa and further in view of Tegenfeldt, (3) the rejection of claim 32 under 35 U.S.C. 103(a) as being unpatentable over Fisher as evidenced by Chaudhry in view of Kigawa and further in view of Gite, and (4) the rejection of claim 68 under 35 U.S.C. 103(a) as being unpatentable over Fisher in view of Kigawa and further in view of Tegenfeldt. In view of the cancellation of claim 127, the rejection based on the combined teachings of Fisher, Chaudhry, Rye, and Thompson currently applies to claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126, and 128-130. Applicant argues that the combined teachings of the cited references do not result in all of the claimed limitations, specifically, the limitation "allowing the nucleic acid binding enzyme to bind non-specifically to the nucleic acid polymer and translocate along the nucleic acid polymer" (see pages 14-15). This argument was not persuasive, because as discussed above, the term "allowing" only requires that the nucleic acid binding agent is capable of or not prevented from binding non-specifically to and translocating along the nucleic acid polymer. In other words, the term "allowing" does not require that the nucleic acid binding agent actually binds to and translocates along the nucleic acid polymer. As discussed above, the method of Fisher does not prevent or prohibit non-specific binding between the nucleic acid polymer and the nucleic acid binding enzyme (S1 nuclease or P1 nuclease) or translocation of the nucleic acid binding enzyme along the nucleic acid polymer. Furthermore, regarding claim 68, it is inherent that the P1 or S1 nuclease taught by Fisher binds at least transiently to the nucleic acid polymer before the nucleic acid tag molecule binds specifically to the nucleic acid polymer. Therefore, the combined teachings of cited references result in all of the limitations of the rejected claims, and the

rejections under 35 U.S.C. 103(a) have been maintained.

Conclusion

12. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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